REMARKS

In this Amendment, claims 1-2, 4-5, 8 – 11, and 13 - 21 have been canceled without prejudice. Claims 3, 6,7 and 12 are withdrawn. Claims 22 – 42 have been added. Support for these newly added claims can be found throughout the specification as originally filed on April 28, 2006.

Applicants respectfully reserve the right to pursue any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

It is submitted that the claims, herewith and as originally presented were in full compliance with the requirements of 35 U.S.C. § 112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendment should not give rise to any estoppel.

Reconsideration and withdrawal of the rejections of this application in view of the amendments and remarks herewith, is respectfully requested, as the application is in condition for allowance.

1. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

> The Examiner states, "The species are as follows:
> The compounds in claim 11 and the species of examples 1 -433 at pages 82-418 of the specification.
> Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.
> Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added

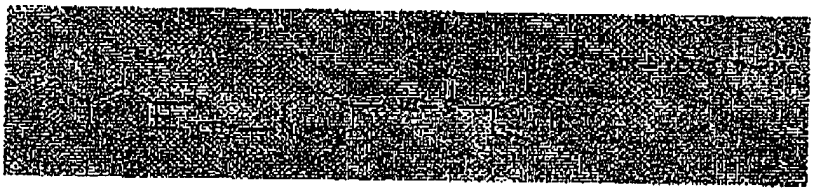
after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).
During a telephone conversation with Greg Butler on 8/27/08 a provisional election was made with traverse to elect the species of "methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridine-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate", which is the second species from the top in claim 11. Affirmation of this election must be made by applicant in replying to this Office action. Claims 19-20 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.".

Applicant's attorney had a telephonic interview with the Examiner on August 27, 2008, during which 5-(aminomethyl)-6-isobutyl-2-4-(methylphenyl)nicotinic acid was elected as the species and is the second species from the top in claim 11. Applicants affirm the election of species:
5-(aminomethyl)-6-isobutyl-2-4-(methylphenyl)nicotinic acid. Please note "methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridine-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate" is the third species from the top in claim 11.

2. The Examiner states, "Claims 1-5, 7, 9, 12, 15-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Schoen et. al. the compounds of examples 69, 70 and 71. At column 159, lines 1-15, column 160, lines 1-20, and at column 160, lines 35-55, see the compounds of examples 69-71 respectively.".

Claims 1-5, 7, 9, 12 and 15 – 16 have been canceled or withdrawn. The newly added claims are not anticipated by Schoen et al. because they are clearly distinguished from Schoen et al. since R^4 has been limited to an amino group.

3. The Examiner states, "Claims 1-5, 7, 9, 12, 15-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Hcaplus 1997:9205. Hcaplus 1997:9205 discloses the instant compounds.".



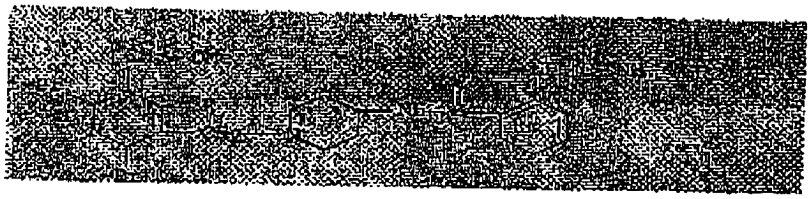
Claims 1-5, 7, 9, 12 and 15 – 16 have been canceled or withdrawn. The newly added claims are not anticipated by Hcaplus et al. because they are clearly distinguished from Hcaplus et al. since R^4 has been limited to an amino group and X is not a hydrogen atom.

4. Claims 13-14 rejected under 35 U.S.C. 103(a) as being unpatentable over Schoen et. al.

Schoen et. al. teaches the instant compounds of examples 69, 70 and 71. At column 159, lines 1-15, column 160, lines 1-20, and at column 160, lines 35-55, see the compounds of examples 69-71 respectively.

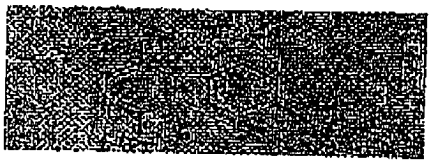
The difference between the prior art compounds and the claimed compositions is the teaching of a compound mixed with a pharmaceutically acceptable carrier in the instant application versus a compound that is taught in the prior art that is not mixed with a pharmaceutically acceptable carrier. It would have been obvious to one of ordinary skill in the art to make pharmaceutical compositions out of these compounds because it is obvious to place these compounds in ethanol or another, non-toxic solvent in which they are soluble, because they are soluble in ethanol or other non-toxic solvents. Accordingly, the compositions and process of making them are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compositions and process of making them over those of the prior art compounds.

Claims 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hcaplus 1997:9205Hcaplus 1997:9205 teaches the instant compound,



The difference between the prior art compounds and the claimed compositions is the teaching of a compound mixed with a pharmaceutically acceptable carrier in the instant application versus a compound that is taught in the prior art that is not mixed with a pharmaceutically acceptable carrier. It would have been obvious to one of ordinary skill in the art to make pharmaceutical compositions out of these compounds because it is obvious to place these compounds in ethanol or another, non-toxic solvent in which they are soluble, because they are soluble in ethanol or other non-toxic solvents. Accordingly, the compositions and process of making them are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compositions and process of making them over those of the prior art compounds.

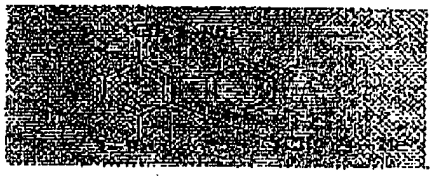
Claims 1, 3-7, 12,15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heaplus 2001:278024 in view of Patani et. al. Hcaplus



2001:278024 teaches the compound,

The difference between the prior art compound and the instantly claimed compounds is the teaching of the X moiety as methyl in the prior art rather than hydrogen in the instant compounds. Methyl can be a bioisosteric replacement for hydrogen. See page 3152 of Patani et. al. The prior art compound and the instant compounds are bioisosteres of each other. Bioisosteres are defined as compounds that elicit similar biological activity because of their similar physicochemical properties. See page 3148 of Patani et. al. It would have been obvious to one of ordinary skill in the art to modify the prior compound which is a bioisostere of the instant compound and which has pharmaceutical use to obtain the instant compound. For instance, see the compound,

Accordingly, the instant compounds are deemed unpatentable therefrom in the absence of a showing of unexpected chemical results for the claimed polymorphs over those of the bioisosteres.



As stated above, claims 1-5, 7, 9, 12 and 15 – 16 have been canceled or withdrawn. The newly added claims are not obvious by Hcaplus et al. in view of Patani et. al. because they are clearly distinguished from since R^4 has been limited to an amino group and X is not a hydrogen atom. Applicants respectfully request reconsideration.

5. Claims 1- 16, 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the compounds of formula I and Ia with R1 equal to isobutyl, neopentyl, Q equal to a bond, L and La equal to methylene, X and Xa equal to carboxy, R3 equal, to optionally substituted phenyl, and R4 equal to NI-12, does not reasonably provide enablement for using the compounds of formula I and Ia, with R1, Q, L, La, X, Xa, R3, and R4 equal to all other moieties claimed. The specification does not enable any skilled

pharmacologist or physician to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized below.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1)the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art 6) the amount of direction provided by the inventor 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

a) Determining if any particular claimed compounds of formula I or Ia with R1, Q, L, La, Xa, X, R3, and R4 equal to all other moieties claimed other than those noted to be enabled above, would be active would require synthesis of the substrate and subjecting it to testing with Applicants' dipeptidyl peptidase IV inhibitory activity assay. Considering the large number of compounds to be made this is a large quantity of experimentation. b) The direction concerning the claimed compounds is found at pages 419-421, which merely states Applicants' intent to make and use such compounds. c) In the instant case none of the working examples contains any radicals R1, Q, L, La, Xa,X, R3, and R4 equal to moieties other than those noted to be enabled above.

d) The nature of the invention is inhibition of dipeptidyl dipeptidase -IV and treatment of human diseases with Applicants' compounds. This involves physiological activity. e) There is no reasonable basis for the assumption that the myriad of compounds embraced the present formulas (I) and Ia will all share the same biological properties. The diverse claimed radicals are chemically nonequivalent and there is no basis in the prior art for assuming in the non-predictable art of pharmacology that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724 (compounds actually tested which demonstrated the asserted psychomotor stimulatory and anti-convulsant properties were those having the 3,4-dichlorophenyl substituent at the 2-position on the thiazolidone nucleus not sufficient for enablement of any heterocyclic radical at the same position). *In re Fouche,* 169 USPQ 429 at 434 (a Markush group including both aliphatic and heterocyclic members not enabled for the use of those compounds within the claim having heterocyclic moieties.) *In re CAVALLITO AND GRAY,* 127 USPQ 202 (claims covering several hundred thousand possible compounds, of which only thirty are specifically identified in appellants' application, not enabled unless all of the thirty specific compounds disclosed had equal hypotensive potency because that fact would strongly indicate that the potency was derived solely from the basic structural formula common to all of them. A wide variation in such potency would suggest that it was due in part to the

added substituents and might be eliminated or even reversed by many of the possible substituents which had not been tried.)

0 The artisan using Applicants' invention to treat diseases with the claimed compounds would be a physician with a MD degree and several years of experience. He would be unaware of how to predict *a priori* how a changing a heterocyclic ring would affect biological activity. In view of the divergent rings with varied basicity, steric hindrance, and polarisability, the skilled physician would indeed question the inclusion of such fused rings, commensurate in scope with these claims. g) Physiological activity, is well-known to be unpredictable, *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright,* 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck,* 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all of millions of compounds of formula (I) and Ia. Thus, the scope is very broad. The present claims embrace various heterocyclic radicals, which are not art-recognized as equivalent. The specific compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright,* 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer,* 146 USPQ 218 (1965); *In re Colianni,* 195 USPQ 150, *Ex parte Formal,* 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo,* this is still an experimental science. For a compound to be a prodrug, it

must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is found at page 51, lines 12-34, and at page 53, lines 1-10 c) There is no working example of a prodrug of a compound the formulas I. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part 1", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formulas I, as well as the presently unknown list of potential prodrug derivatives embraced by claim 12.

Applicants have canceled claim 1 and have added corresponding claim 22 which has been limited in scope to be commensurate with that of the compounds of the Examples, which is similar to the scope of "Compound D" on pages 43-49 in the specification. In addition Applicants have added claims 37 -42.

Furthermore, Applicants have withdrawn claim 12 and added claims 30, 32, 34 and 35 which correspond to canceled claims 13, 15, 19 and 20, respectively. The term "prodrug thereof" is not in the language of newly added claims 30, 32, 34 and 35. Applicants respectfully request reconsideration.

In view of the remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested.

FEE AUTHORIZATION

Applicant requests a two-month extension of time to file the within response. The commissioner is authorized to charge the extension fee and any other fees associated with this submission to our deposit account, no. 04-1105, reference 66540(46590). Any overpayment should be credited to said deposit account.

Dated: March 20, 2009

Respectfully submitted,

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